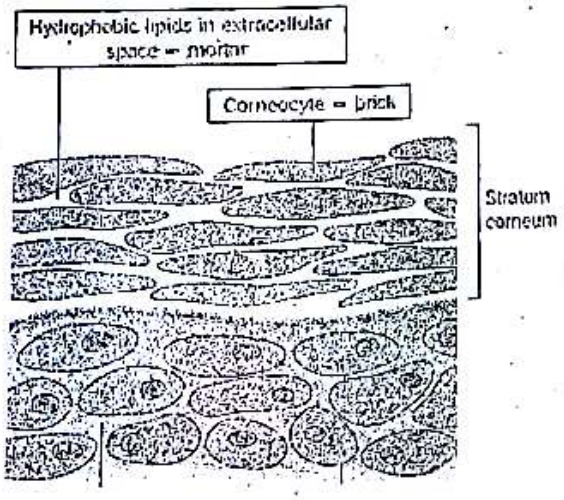
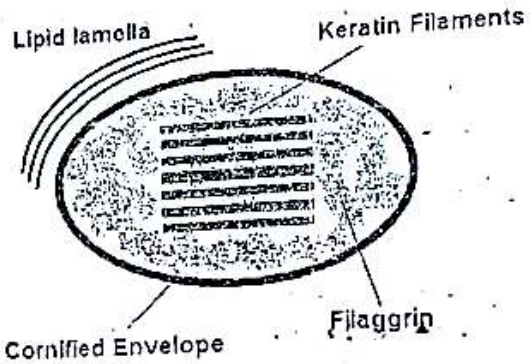
Skin Barrier

The stratum corneum:

- the thin outer layer of the epidermis
- consists of corneocytes (composed mainly of aggregated keratin filaments "protein" enclosed in a cornified envelope) surrounded by an extracellular lipids (organized as multiple lamellar bilayers)
  - Lipids prevent excessive loss of water from the body and block entry of most substances (other than those that are lipid-soluble and of low molecular weight)

The "two-compartment" system = The "bricks and mortar" system:





- The stratum corneum is made of **proteins** and **lipids** مهم جداً
- Stratum corneum is typically comprised of about 20 corneocyte cell layers (corneocytes = bricks)
- Corneocytes are surrounded by a highly cross-linked sheath "the **cornified envelope**" while the cell interior is packed with keratin filaments embedded in a matrix composed mainly of **filaggrin** protein and its breakdown products (**natural moisturizing factors, NMFs**)
- **Hydrophobic lipids** within the **extracellular** space are organized into **lamellar membranes** that surround the corneocytes (lipids = mortar)
- The three major extracellular lipids are **ceramides, cholesterol and free fatty acids** and are arranged in a critical (1 : 1 : 1) molar ratio
  - **Ceramides**: 50% of the total stratum corneum lipid mass
  - **Cholesterol**: 35–40% of stratum corneum lipids
  - **Free fatty acids**, which account for 10–15% of stratum corneum lipids

Cells of the granular cell layer contain	
Keratohyaline granules ↓ **Protein**	**Lamellar bodies "Odland bodies"** ↓ **Lipids**
Enzymatic transformation of **profilaggrin → filaggrin** (responsible for aggregation of keratin filaments into macrofibrils → cross-linked to the cornified cell envelope → responsible for proper formation of compact squamous cells By reaching the skin surface, filaggrin is degraded to free amino acids - the basic components of a highly absorbent complex called **natural moisturizing factor (NMF)**	Contain... • precursor lipids • processing "lipolytic/hydrolytic" enzymes o Glucosylceramides → *β-glucocerebrosidase* → ceramides o Sphingomyelin → *acidic sphingomyelinase* → ceramides o Cholesterol sulfate → *steroid sulfatase* → cholesterol o Phospholipids → *phospholipase* → free fatty acids Aim: conversion of polar precursors to **non-polar** lipids and their organisation into lipid layers
	Lamellar bodies also contain **proteases** and antiproteases that orchestrate the digestion of corneo-desmosomes, allowing **corneocyte shedding**

Cholesterol sulfate → steroid sulfatase → cholesterol

cholesterol sulphate

☆ 6% of epidermal lipids in the granular layer

☆ 3% of epidermal lipids in the stratum corneum

cholesterol sulphate (in the stratum corneum)

☆ stabilizes lipid bilayers

☆ reduces the activity of serine proteases responsible for cleaving desmosomes

As we go up in the stratum corneum, increasing activity of membrane-based steroid sulphatase at the corneal–granular layer junction ⇨ rise in epidermal cholesterol level ⇨ triggers stratum corneum intercellular lipid **bilayer disintegration and desquamation**

Ichthyoses

General features:

- **A group of disorders of cornification/keratinization (abnormal differentiation and desquamation of the epidermis ⇨ defective epidermal barrier**
- **Characterized clinically by ⇨ generalized scaling of the skin (the Greek root "ichthy" meaning fish السمكية)**
- **Uncommon disorders**

Diagnostic approach to a case of ichthyosis:

History	Examination	Investigations

(1) History:

Family history:

- ☆ essential for recognizing the **inheritance pattern**
- ☆ patients whose **parents are clinically unaffected** may have
  1. a **recessive** ichthyosis (especially in the setting of consanguinity and/or affected siblings)
  2. a **dominant** ichthyosis due to a **"new" mutation**.
  3. (for male patients) ⇨ an X-linked recessive ichthyosis (where their mother may be an asymptomatic carrier and male relatives could potentially be affected

Age of onset:

- ☆ at birth
- ☆ later in life

(2) Examination:

General examination: to determine whether ichthyosis is ..

- ☆ limited to the skin, **or**
- ☆ part of a multisystem disorder

Local (Skin) examination:

- **Scales** مهم جداً
  - ☆ characteristics
  - ☆ distribution
- **Presence or absence of** erythroderma, blistering, abnormalities of cutaneous adnexa

Examination of both parents (even in a seemingly sporadic case) may reveal valuable diagnostic hints such as an epidermal nevus representing a mosaic presentation of epidermolytic ichthyosis epidermolytic

↑incidence → ↓ severity

Classification of ichthyoses:

(A) Congenital ichthyoses

Common ichthyoses:

- Ichthyosis vulgaris
- X-linked recessive ichthyosis (steroid sulphatase deficiency)

Non-syndromic AR congenital ichthyoses: من فئة الـ AR

- Lamellar ichthyosis
- Congenital ichthyosiform erythroderma (CIE) } Similar clinically They are spectrum
- Harlequin ichthyosis

Keratinopathic ichthyoses:

- Epidermolytic ichthyosis (Bullous ichthyosiform erythroderma)
- Superficial epidermolytic ichthyosis (Ichthyosis bullosa of Siemens)
- Ichthyosis hystrix Curth–Macklin

Ichthyosiform syndromes (Syndromic ichthyoses): تعرف بسبب defect & feature (C/P)

- Netherton's syndrome (ichthyosis linearis circumflexa)
- Sjögren–Larsson syndrome
- Neutral lipid storage disease (syn. Chanarin–Dorfman syndrome)
- Refsum's disease
- Trichothiodystrophy with ichthyosis (IBIDS, PIBIDS)

(B) Acquired ichthyosis مهم جداً

Occurs later in life

Association with …

- **Drugs** e.g. nicotinic acid, hypocholesterolaemic agents, maprotiline
- **Chronic diseases** e.g. hepatic disease, renal failure, thyroid and parathyroid disease
- **Malabsorption** states ↓ lipid absorption
- **Inflammatory** disorders e.g. sarcoidosis,
- **Infections** e.g. leprosy مهم جداً, acquired immune deficiency syndrome (AIDS)
- **Malignancies** e.g. lymphoma مهم جداً

In any type of hereditary ichthyosis…

1. **Synonyms:**
2. **Epidemiology: Incidence/ prevalence:**
3. **Pathogenesis:**
   - **Mode of inheritance:**
   - **Defect:**
4. **Clinical Features:**
   - **Age of presentation:** at birth / later in life (within 3 years maximum) + Sex:
   - **Symptoms:** ± pruritus (dry skin)
   - **Skin manifestations:**
     - *Dry skin:*
     - *Scaling:*
       - Characteristics
       - Distribution
   - **Other associated features: if present**
5. **Course:**
6. **Investigations:**
   - *Histopathology:*
   - *Electron microscopy (Ultrastructural features):*
   - *Laboratory studies* e.g. steroid sulfatase enzyme analysis (steroid sulfatase deficiency)
   - *Immunohistochemistry:*
   - *Molecular diagnosis (genetic testing):*

Ichthyosis or not? congenital
If ichthyosis: hereditary or acquired?
If hereditary: which type?

7. **Differential Diagnosis:**
   - Other causes of dry skin (xerosis)
   - Acquired ichthyosis
   - Other types of hereditary ichthyosis
8. **Treatment:**

Aim of treatment: reduction of scaling (hyperkeratosis)
Therapy is symptomatic

- **Topical** management: emollients, keratolytics and retinoids
- **Systemic** treatment: most (but not all) ichthyoses respond to oral retinoids (treatment is initiated at low doses and dose modified according to clinical response)
  - side effects must be carefully considered because of the chronic nature of these conditions

Ichthyosis vulgaris

Synonyms:
- Ichthyosis simplex
- Autosomal dominant ichthyosis

Epidemiology: Incidence/ prevalence:
- the **most common** type of ichthyosis (prevalence: 1 in 250 individuals)

Pathogenesis:

Mode of inheritance: autosomal dominant (AD)
autosomal **semi-dominant**
- heterozygous mutations (mutations in only 1 of the 2 alleles) ⇨ mild ichthyosis *1
- homozygous mutations (mutations in both alleles) ⇨ more severe ichthyosis **

Defect:
Loss-of-function mutations in the **filaggrin (FLG) gene**

FLG encodes profilaggrin (a component of the keratohyalin granules) ⇨ cleaved into filaggrin peptides……
- aggregate keratin intermediate filaments, cross-linked to the cornified cell envelope and are responsible for proper formation of compact squamous cells
- degraded into water-retaining amino acids (a natural moisturizer)

FLG deficiency ⇨ impaired squamous cell formation, transepidermal water loss, and a liability to develop inflammatory responses upon exposure to allergens and haptens (this explains the **association** of **FLG mutations** with **atopic dermatitis** as well as ichthyosis vulgaris مهم جدا)

Clinical Features:

Age of presentation: usually **not** evident at birth (appear during *infancy* or *early childhood*)

Symptoms: ± pruritus
☆ Symptoms and severity depend on ***season and climate***
- improving during the summer and with higher humidity
- worsening in a **dry, cold environment** الشتا

Skin manifestations:

1. ***Dry skin:***
2. ***Scaling:***
   - Characteristics: (mild to moderate) **fine, white** مهم جداً, flaky scales
   - Distribution: مهم جداً **extensor** surfaces of the extremities
     - ☆ In more severe disease, scaling occurs on the trunk, scalp, forehead and cheeks
     - ☆ The **groin and flexural** areas are **spared** مهم جداً (because of increased humidity)

Other associated features:

1. **atopic triad: asthma, hay fever and atopic dermatitis** مهم جداً

> ***Correlation between atopic dermatitis and ichthyosis vulgaris***
> ☆ at least 25–50% of patients with ichthyosis vulgaris have atopic dermatitis ⇨ can obscure the characteristic sparing of the flexures
> ☆ approximately 10–15% of individuals with atopic dermatitis also have ichthyosis vulgaris
> ☆ both due to mutation in FLG gene

2. Mild **hyperkeratosis of the palms and soles** ⇨ accentuated skin markings (**hyperlinearity** مهم جداً)
3. **keratosis pilaris**

Course:

- ☆ progressive during childhood
- ☆ usually improves with age

Investigations:

- ☆ ***Histopathology:***
  - Mild orthokeratotic **hyperkeratosis**
  - Diminished or absent granular layer (**hypogranulosis**) مهم جداً
- ☆ ***Electron microscopy:***
  - approximately 30–50% of affected individuals have **no detectable granular layer** and **no keratohyalin granules**
  - others have **structural abnormalities in keratohyalin granules**
- ☆ ***Immunohistochemistry:*** diminished or absent filaggrin staining
- ☆ ***Molecular diagnosis:*** mutation in filaggrin gen.

Differential Diagnosis:

1. Other causes of **dry skin (xerosis)**: may simulate ichthyosis vulgaris (both can be associated with atopic dermatitis)
2. Other types of **hereditary ichthyosis**: e.g. X-linked ichthyosis ..
   - the inheritance pattern
   - maternal history of delayed or prolonged labor
   - larger, darker scales and involvement of the neck and other flexures
   - cryptorchidism
3. **Acquired ichthyosis** is distinguished by
   - development later in life
   - association with conditions such as malnutrition, infections (e.g. leprosy), neoplasms (e.g. lymphoma) and inflammatory disorders (e.g. sarcoidosis).

Treatment:

Aim of treatment: reduction of scaling

- **Topical treatments:**
  - ☆ *Emollients* and humectants: (the mainstay of treatment) Vasln.
    - o Preparation containing
      - ceramides and other lipids (???)
      - urea
  - ☆ *Keratolytics* e.g. α-hydroxy, lactic and salicylic acids (care: salicylate toxicity)
  - ☆ Topical *retinoids*: decrease scaling (side effect: irritation of the skin → limits their use)
  - ☆ *Vitamin D analogues* are ineffective
- **Systemic treatment:**
  - ☆ Systemic *retinoids* e.g. acitretin or isotretinoin may be used (but rarely necessary)
- **General measures:** use of moisturizing cleansers and humidifiers

Acitretin ↓ keratinocyte differation

o tretinoin ↓ secretion.

deficiency of steroid sulfatase

Steroid sulfatase deficiency

Synonyms:

- X-linked recessive ichthyosis

Epidemiology: Incidence/ prevalence:

Worldwide incidence: 1 in 2000 - 1 in 9500 **male** births (**less common** than ichthyosis vulgaris)

Pathogenesis:

Mode of inheritance: X-linked recessive (**XLR**)

- transmitted by asymptomatic **female carriers**
- Although steroid sulfatase activity is measurably reduced in 85% of female carriers, the remaining activity seems sufficient to prevent any skin manifestations.
- almost exclusively affects **boys and men**

Defect:

- Decreased or absent **steroid sulfatase (STS)** activity
- Caused by a **deletion** of the entire STS gene (90% of patients) or **inactivating mutations** (in others)
- Steroid sulfatase deficiency ⇨ impaired hydrolysis of **cholesterol sulfate** and dehydroepiandrosterone sulfate (DHEAS) ⇨

to tested

DHEA → estrogen

I) in the **epidermis** ⇨ accumulation of **cholesterol sulfate**

- *cholesterol sulphate (in the stratum corneum)*
  - ☆ stabilizes lipid bilayers
  - ☆ reduces the activity of serine proteases responsible for cleaving desmosomes
- In XLR ichthyosis, cholesterol sulphate accounts for 12–30% of stratum corneum lipids (normally: 3 %) ⇨ **persistence of desmosomes and retention hyperkeratosis**

II) in the fetal placenta (in women pregnant with an affected fetus) ⇨ inadequate deconjugation of DHEAS (which is necessary for estrogen synthesis) ⇨ low or absent levels of estrogen in the urine and amniotic fluid ⇨ labor fails to initiate spontaneously or progress (due to insufficient dilation of the cervix)
This can be partially overcome by oxytocin administration, often necessitating cesarean section

Clinical Features:

Age of presentation: during the neonatal period (in ~90% of affected boys)

Symptoms: ± pruritus

☆ Symptoms and severity depend on *season and climate*

- The ichthyosis tends to improve in the summer

Skin manifestations:

- **during the neonatal period:** starts with mild erythroderma and generalized peeling, with exfoliation of large, translucent scales
- **later on (during infancy):** the typical scales .....
  - Characteristics: polygonal, dark-brown, large, adherent
  - Distribution: مهم جدا
    - ☆ distributed **symmetrically** on the **extremities, trunk and neck**
    - ☆ the neck is almost always involved **"dirty neck disease"**
    - ☆ **flexural** areas may or may not be affected
    - ☆ The **palms, soles and face** are characteristically **spared** (with the exception of the **pre-auricular** area ⇨ pathognomonic feature)

Other associated features:

1. Asymptomatic **corneal opacities** (10–50%)
2. **Other ocular abnormalities** e.g. ~~deuter~~anopia (green color-blindness) are rare
3. Male patients have a 20-fold increased incidence of **cryptorchidism** and are at higher risk for developing **testicular cancer** and **hypogonadism**
4. **Others:** Seizures, reactive psychological disorders, attention deficit disorder, developmental delay, pyloric hypertrophy, a congenital defect in the abdominal wall and acute lymphoblastic leukemia

Course:

Does not significantly subside with age (in contrast to ichthyosis vulgaris)

Investigations:

☆ *Histopathology:*

- hyperkeratosis or parakeratosis
- a normal or slightly thickened granular layer
- follicular hyperkeratosis may be present

☆ ***Electron microscopy:***

- ~~increased size and number of keratohyalin granules~~ Structural abnormalities: lamellar gran
- in the stratum corneum, desmosomes are retained and cells contain a large number of melanosomes. cellline bod

☆ ***Molecular diagnosis:*** detection of gen defect.

NB. non-invasive prenatal diagnosis through decreased serum estriol levels and the presence of non-hydrolyzed sulfated steroids in maternal urine

Differential Diagnosis:

1. Other causes of dry skin (xerosis):

2. Other types of hereditary ichthyosis: e.g. Ichthyosis vulgaris
   - sparing of flexural areas (including the neck)
   - association with hyperlinear palms and keratosis pilaris
3. Acquired ichthyosis is distinguished by
   - development later in life
   - association with conditions such as malnutrition, infections (e.g. leprosy), neoplasms (e.g. lymphoma) and inflammatory disorders (e.g. sarcoidosis).

Treatment:

عادى جداً

باختصار

- Topical humectants (in particular propylene glycol), keratolytics and retinoids (alone or in combination)
- Vitamin D analogues are disappointing and cause significant irritation
- Systemic retinoids are rarely necessary

Non-syndromic AR congenital ichthyosis (ARCI)

ALL...

- Rare ↓incidance. ⇝ ↑severity
- AR inheritance
- Same / similar defect(s)
- Present at birth = congenital
- Spectrum of clinical features
- Severe (in comparison to common ichthyoses) ⇒ bad prognosis
- Similar treatment

Congenital ichthyosiform erythroderma (CIE)	Lamellar ichthyosis (LI)	Harlequin ichthyosis (HI)
The commonest	Less common	Rare
1 : 100 000–1 : 200 000	1 : 200 000–1 : 300 000	Rare
Present at birth with **colloidon membrane** ⇨ **scales**		Born in a **hard thickened stratum corneum** sheath ⇨ **large, yellow, adherent plates**
Erythroderma	NO/minimal erythroderma	
Fine white scales	Large brown scales	

Lamellar ichthyosis (LI)

Synonyms:

- Ichthyosis congenita type 2
- Non-erythrodermic autosomal recessive lamellar ichthyosis

Epidemiology:Incidence/ prevalence:

- LI occurs worldwide
- estimated prevalence of 1 in 200 000 to 1in 300 000 live births

Pathogenesis:

Mode of inheritance: Autosomal recessive

Steroid sulfatase deficiency

Synonyms:

- X-linked recessive ichthyosis

Epidemiology: Incidence/ prevalence:

Worldwide incidence: 1 in 2000 - 1 in 9500 **male** births (**less common** than ichthyosis vulgaris)

Pathogenesis:

Mode of inheritance: X-linked recessive (**XLR**)

- transmitted by **asymptomatic female carriers**
- Although steroid sulfatase activity is measurably reduced in 85% of female carriers, the remaining activity seems sufficient to prevent any skin manifestations.
- almost exclusively affects **boys and men**

Defect:

- Decreased or absent **steroid sulfatase (STS)** activity
- Caused by a **deletion** of the entire STS gene (90% of patients) or **inactivating mutations** (in others)
- Steroid sulfatase deficiency ⇨ impaired hydrolysis of **cholesterol sulfate** and dehydroepiandrosterone sulfate (**DHEAS**) ⇨

I) in the **epidermis** ⇨ accumulation of **cholesterol sulfate**

Cholesterol sulphate (in the stratum corneum)

- ☆ stabilizes lipid bilayers
- ☆ reduces the activity of serine proteases responsible for cleaving desmosomes

- In XLR ichthyosis, cholesterol sulphate accounts for 12–30% of stratum corneum lipids (normally: 3 %) ⇨ **persistence of desmosomes and retention hyperkeratosis.**

II) in the **fetal placenta** (in women pregnant with an affected fetus) ⇨ inadequate deconjugation of **DHEAS** (which is necessary for estrogen synthesis) ⇨ low or absent levels of estrogen in the urine and amniotic fluid ⇨ **labor fails** to initiate spontaneously or progress (due to insufficient dilation of the cervix). This can be partially overcome by oxytocin administration, often necessitating **cesarean section**

- **The degree of palmoplantar keratoderma** is variable and can range from accentuated skin markings to severe thickening with cracking and fissuring.
- **Secondary nail dystrophy** with thickened nail plates and ridging is not uncommon.
- Intra-epidermal constriction of sweat ducts often results in severe **heat intolerance**
- Accumulation of scale in the **external ear canals** can lead to **occlusion, bacterial colonization** and recurrent **infections.**

Course:

☆ **persists** throughout life

☆ LI and other severe forms of ARCI are often **disfiguring**, which may hinder the **psychosocial** development of affected children and adolescents.

Investigations:

☆ ***Histopathology:***
- The histologic abnormalities are **not diagnostic**
- **Massive** orthokeratotic **hyperkeratosis**
- **acanthotic** epidermis, sometimes with psoriasiform or papillomatous hyperplasia

☆ ***Electron microscopy:***
- thin or absent cornified cell envelope ∴ TGM 1 deficiency
- Elongated cholesterol clefts
- variable numbers of translucent lipid droplets in the stratum corneum dd. ABC
  - these findings overlap with those of CIE

☆ ***Laboratory studies*** measuring **transglutaminase-1** activity in cultured keratinocytes

☆ ***Immunostaining*** Transglutaminase-1 deficiency can be detected by immunostaining for and/or assessing the activity of this enzyme in skin biopsy specimens.

☆ ***Molecular diagnosis:***
- Prenatal diagnosis can be performed in families with known mutations from chorionic villus sampling (CVS) or amniocentesis material obtained at an early gestational age

Differential Diagnosis:

1. **Other causes of dry skin (xerosis):**
2. Other types of **hereditary ichthyosis:** هو ده المهم
   - In the **neonatal period** ⇨ **other congenital ichthyoses that present with a collodion membrane**, especially…
     - ☆ CIE
     - ☆ self-healing collodion baby
   - **Later in life**, the large, dark, plate-like scales, ectropion and no discernible erythroderma of LI can be readily distinguished from most **other ichthyoses.**
     - ☆ *Classic CIE* is differentiated by marked erythroderma and small white scales
     - ☆ Some patients exhibit intermediate LI/CIE phenotypes with variable degrees of erythroderma as well as quality and size of scales.
3. **Acquired ichthyosis** is distinguished by
   - development **later** in life
   - **association** with conditions such as malnutrition, infections (e.g. leprosy), neoplasms (e.g. lymphoma) and inflammatory disorders (e.g. sarcoidosis).

Treatment:

- **Neonatal care. (of collodion babies ???)**
- **Systemic treatment:** فى الحالات دى نبدأ بالـ
  - Severe disease often necessitates systemic therapy with **oral retinoids** from **early childhood**
  - **Acitretin** can be very effective in alleviating hyperkeratosis and scaling. Treatment is usually **initiated** at a low dose and then titrated to the minimal effective dose, which is dictated by the course and severity of the disease
  - the benefits of long-term systemic retinoid therapy must be weighed against the **potential toxicities**

A have prob in Keratinization.
A ē Acitritin ⇒ ↑ I C Hg. دلوقتى مضرة اوى

- **Topical management** should always take into consideration the severely impaired desquamation and barrier function of the skin.
  - The use of **keratolytics** is often **limited** due to skin irritation and an increased risk of systemic absorption, especially in children.
  - Topical **vitamin D3 derivatives**, **tazarotene**, and formulations containing **lactic acid** and **propylene glycol** in a lipophilic cream base have been effective.

- **General measures / Management of complications:**
  - **Heat intolerance** can be ameliorated by frequent **moistening** of the skin with water or the use of **air conditioning** and **humidifiers**
  - Severe **ectropion** requires longitudinal ophthalmologic evaluation; surgical repair is sometimes necessary to prevent irreversible corneal damage.

Congenital ichthyosiform erythroderma (CIE)

Synonyms:

- Non-bullous congenital ichthyosiform erythroderma
- Ichthyosis congenita type 1
- Erythrodermic autosomal recessive lamellar ichthyosis

Epidemiology:Incidence/ prevalence:

- slightly **more common than LI**, affecting 1 in 100,000 to 1 in 200,000

Pathogenesis:

Mode of inheritance: Autosomal recessive
(This type of ARCI is clinically and genetically very heterogeneous)

Defect: mutations in

1. TGM1
2. ABCA12
3. OTHERS..: (LI نفس الكلام زى)

يكتب بالتفصيل كما سبق

Clinical Features

- **Age of presentation:** apparent <u>at birth</u>
- **Symptoms:** <u>severe</u> disorder
  - ☆ **<u>milder</u> than classic <u>LI</u>**

- **Skin manifestations:**
  - CIE usually presents **at birth** with a **collodion membrane**, with subsequent evolution into **generalized erythroderma** مهم جداً and **scaling**
  - There is variability in the intensity of erythema as well as the size and type of scale.

(A) In severely affected patients, CIE is characterized by

- intense, bright red erythroderma
- generalized **white, small scales** with a "**powdery**" consistency
  - scales may become larger, darker or plate-like, especially on the extensor surface of the lower extremities
- additional findings such as **ectropion** and **scarring alopecia**
- the **palms and soles** are usually severely affected with a diffuse, fissuring **keratoderma** (that contrasts with the fine, translucent scales elsewhere on the body)

- Patients with milder disease exhibit
  - less intense erythroderma and scaling (although the latter still tends to be generalized)
  - variable palmoplantar involvement

Other associated features: if a spectrum

- The obstruction of sweat ducts and pores often results in hypohidrosis and heat intolerance.
- Secondary nail dystrophy, onychomycosis and digital flexion contractures are not uncommon.
- Severe exfoliative erythroderma can cause metabolic stress in growing children, including substantial energy expenditure through evaporation in the setting of increased transepidermal water loss and failure to meet their high caloric needs can lead to growth retardation.
  - However, most children with CIE have normal growth and development.
- Adults with CIE may have an increased risk of developing cutaneous squamous cell carcinoma (SCC), so longitudinal skin surveillance should be considered

Course: Remains throughout life

Investigations:

The histopathologic and ultrastructural features of CIE are non-diagnostic.

☆ *Histopathology:* Compared to LI,
- there is more parakeratosis (focal or extensive)
- the acanthosis is typically more pronounced and accompanied by hypergranulosis

☆ *Electron microscopy:*
- increased number of lamellar bodies
- accumulation of lipid droplets in the stratum corneum (often more prominent than in LI)
- disorganized intercellular lipid lamellae
  - (these findings overlap with those seen in LI)

☆ *Laboratory studies* measuring transglutaminase-1 activity in cultured keratinocytes

- Immunostaining: TGM-1 deficiency can be detected by immunostaining and/or assessing the activity of this enzyme in skin biopsy specimens.
- Molecular diagnosis:
  - Prenatal diagnosis can be performed in families with known mutations from chorionic villus sampling (CVS) or amniocentesis material obtained at an early gestational age.

Differential Diagnosis:

1. Other causes of dry skin (xerosis):
2. Other causes of erythroderma جلد
3. Other types of hereditary ichthyosis: هو ده اللهم
   - In the neonatal period ⇒ other congenital ichthyoses that present with a collodion membrane, especially...
     - ☆ LI
     - ☆ self-healing collodion baby
   - Pronounced erythroderma and fine white scales in classic CIE differentiate it from classic LI, which is characterized by less erythema, large dark scales and more frequent ectropion, eclabium and scarring alopecia.
     - ☆ However, many intermediate phenotypes with variable degrees of erythema and size and quality of scale exist.
   - Harlequin ichthyosis:
     - ☆ survivors typically develop an extremely severe CIE-like phenotype.
   - Other erythrodermic forms of ichthyosis

4. Acquired ichthyosis is distinguished by
   - development later in life
   - association with conditions as malnutrition, infections (e.g. leprosy), neoplasms (e.g. lymphoma) & inflammatory disorders (e.g. sarcoidosis).

Treatment: As LI (كما سبق - يكتب) + (الأشياء المميزة)

- Erythrodermic patients have a special need for increased intake of fluids, calories, iron and protein to balance substantial loss through the skin, which can be 3–10 times higher than normal.
- Therapy with oral retinoids can reduce scaling, but it is less beneficial in suppressing the erythroderma

Harlequin Ichthyosis

Synonyms:

- **Harlequin baby**
- **Harlequin fetus**
- **Ichthyosis congenita gravior**

- **The most extreme and distinct form of ARCI**
- **"Harlequin"** refers to the resemblance of the facial features and diamond-shaped scales in affected neonates to the costume of the comic servant character with this name.
- Initially called a "harlequin fetus" because of the premature delivery and fatal outcome
- Increasing survival rates due to improved neonatal care and systemic retinoid treatment have resulted in evolution to the terms "harlequin baby" and (currently) "harlequin ichthyosis" (HI).

Epidemiology

Rare

Pathogenesis

- Mode of inheritance: autosomal recessive
- Defect:
  - Biallelic loss-of-function mutations in the **ABC transporter gene** ABCA12 (يكتب بالتفصيل)
  - Truncating mutations and deletions in this gene are usually associated with severe HI
  - Missense mutations may cause a somewhat milder phenotype that overlaps with CIE/LI

☆ Lamellar bodies are absent or improperly formed in patients with HI
☆ Essential epidermal lipids (e.g. glucosylceramide) are abnormally processed and incompletely secreted (or not secreted at all) into intercellular spaces
☆ These changes prevent the formation of lipid bilayers in the stratum corneum and result in massive hyperkeratosis and a severe breakdown of the permeability barrier.

Clinical Features

- **Age of presentation:** apparent **at birth**
- **Symptoms:** severe disorder
- **Skin manifestations:**
  - Individuals with HI are usually **born prematurely** (mean gestational age, 35 weeks) and often **die within a few days or weeks because of *respiratory insufficiency*** مهم جداً or ***sepsis***
  - Affected neonates are encased in a **hard, armor-like, tremendously thickened stratum corneum** that results in **severe immobilization** and **restricts ventilation**
  - Shortly after birth, the hyperkeratotic cast **cracks** and forms **large, yellow, adherent plates** separated by broad, deep, intensely red **fissures**

Other associated features:

- **Increased transcutaneous loss of water** and heat results in dehydration, electrolyte imbalances (e.g. hypernatremia) and temperature instability (may impede recognition of skin infections or sepsis, which are promoted by the large fissures)

- **The tautness of the skin** results in marked eversion of the eyelids (ectropion) and lips (**eclabium**), rudimentary development of ear and nasal cartilage, and sometimes microcephaly, giving the face an extremely distorted appearance.
  - Eclabium and taut facial skin **prohibit effective suckling** by the infant.

- The **hands and feet** are edematous and swollen, often covered by a mitten-like casing.
  - Although the digits are well developed, **autoamputation** due to constricting skin bands occasionally occurs.

- **Eyelashes and eyebrows** are usually missing (scalp hair may be present)

  - All **survivors** develop a severe, **exfoliative ichthyosiform erythroderma**, a painful palmoplantar keratoderma; dystrophic nails (e.g. small, thickened) and poor hair growth

Complications

- recurrent skin infections
- reduced sweating with heat intolerance
- ocular problems related to persistent ectropion
- chronic constipation
- joint contractures
- affected children often have delayed growth and development (especially of motor skills) BUT intelligence is typically normal

Course:

- Patients often **die within a few days or weeks** because of ***respiratory insufficiency*** مهم جداً or ***sepsis***
- Over the past two decades, improved prenatal care and oral retinoid therapy have led to **prolonged survival** in an increasing number of HI patients. More than half of affected individuals now live beyond the neonatal period, with the oldest HI patient to date being 25 years of age

Investigations:

☆ ***Histopathology:***

- The histologic hallmark ⇨ **extraordinarily thickened and compact orthokeratotic stratum corneum**
- **parakeratosis** is occasionally observed
- Hair follicles and sweat ducts ⇨ prominent **hyperkeratotic plugging**

☆ ***Electron microscopy:***

- abnormal or missing lamellar bodies in the granular layer
- absent extracellular lipid lamellae
- presence of lipid inclusions or remnant organelles in the stratum corneum
  - ☆ (**similar** to findings in patients with **CIE**)
- Hair follicles show concentric accumulation of keratotic material around hair shafts

☆ ***Molecular diagnosis:*** V.Imp

- Prenatal molecular testing (as early as the 10th week of gestation with CVS)

Differential Diagnosis:

The clinical presentation of harlequin ichthyosis at birth is striking and highly characteristic

1. Other causes of **dry skin (xerosis)**:

2. Other types of **hereditary ichthyosis**: هو ده المهم
   - Hyperkeratosis and associated abnormalities, such as ectropion and eclabium, are usually much milder in **collodion babies**
   - The clinical findings in children and adults with **HI overlap with severe forms of CIE**

3. **Acquired ichthyosis** is distinguished by
   - development **later** in life
   - association with conditions as malnutrition, infections (e.g. leprosy), neoplasms (e.g. lymphoma) & inflammatory disorders (e.g. sarcoidosis).

Treatment

HI remains a **life-threatening** and often **fatal** disorder, and survivors require long-term multidisciplinary management.

During the neonatal period, intensive care is needed to provide sufficient nutrition, monitor and manage body temperature, correct fluid and electrolyte imbalances, and prevent and treat respiratory dysfunction, pneumonia or sepsis. Severe ectropion necessitates ophthalmologic care.

Infants should be kept in humidified incubators and treated **topically** with light emollients.

Early administration of systemic retinoids, in particular acitretin (usually with an initial dose of 1 mg/kg/day), has been shown to result in shedding of the large, keratotic plates within weeks as well as improvement of the ectropion and eclabium.

Epidermolytic ichthyosis (EI)

Synonyms:

- Bullous congenital ichthyosiform erythroderma (Brocq)
- Epidermolytic hyperkeratosis
- Bullous ichthyosis

Epidemiology

Estimated worldwide prevalence of 1 in 200 000 to 1 in 300 000

Pathogenesis

Mode of inheritance: autosomal dominant

✓ About 50% of all cases occur sporadically (reflecting new mutations)

Defect:

Mutations in the genes encoding keratin 1 (**KRT1**) & keratin 10 (**KRT10**)

- These keratins are expressed in the differentiated **spinous and granular** (فوق) layers of the epidermis ⇨ (sites of disease pathology)
- Mutations disturb keratin alignment, oligomerization and filament assembly, thus weakening the cytoskeleton, compromising the mechanical strength and cellular integrity of the epidermis, and leading to **cytolysis and blistering.**
- Epidermal acanthosis and hyperkeratosis result from **hyperproliferation, decreased desquamation** and other factors.
- The **barrier function** of the skin is markedly disturbed, leading to increased transepidermal water loss and bacterial colonization of the stratum corneum.

NB

KRT1 mutations are usually associated with severe palmoplantar *keratoderma*

KRT10 mutations spare the palms and soles because this gene is **not** expressed in these locations

Clinical Features

Age of presentation: at birth

Skin findings:

1. BI presents at birth with erythroderma, peeling, erosions and widespread areas of denuded skin
2. Later during infancy ⇨ hyperkeratosis develops
3. Over time:
   - Skin fragility, blistering and erythema decrease
   - severe hyperkeratosis prevails
   - **Ridges** along skin lines are common in **flexures**
   - hyperkeratosis over the **extensor** surfaces of the joints forms a **cobblestone** pattern
     - ✓ However, patients may still periodically shed large plates of superficial epidermis, revealing a tender, erythematous base

Associated features / complications:

- *In the neonatal period:*
  - Sepsis & **fluid and electrolyte imbalances** can be life-threatening
- *Later in life:*
  - EI is **disfiguring** and has tremendous impact on **patients' quality of life** and **social** interactions.
  - Episodes of **blistering** and secondary skin **infections**
  - The disorder is accompanied by a **pungent body odor**
  - Occasionally associated with **posture and gait abnormalities**
  - Angular cheilitis
  - severe scalp involvement leading to encasement of hair shafts and hair loss

Epidermolytic nevi (mosaic epidermolytic ichthyosis)

- The mosaic form of EI
- unilateral or bilateral **streaks of hyperkeratosis** that follow the lines of Blaschko
- **Extensive** involvement with marked hyperkeratosis leading to protruding, porcupine-like spines "**ichthyosis hystrix**" ⇨ a descriptive term rather than the name of a distinct disorder
- caused by a **postzygotic mutation** in KRT1 or KRT10 that arises during embryogenesis
- If this mutation involves gonadal cells, it can potentially be transmitted to the patient's offspring, resulting in fullblown, generalized disease
- **Examination of both parents** of a child with sporadic EI is therefore recommended.

Investigations:

Highly characteristic structural and ultrastructural abnormalities allow EI to be distinguished from other congenital ichthyoses

Histopathology

1. dense orthokeratotic hyperkeratosis
2. hypergranulosis
3. prominent acanthosis
4. cytolysis of the suprabasal and granular layers leading to small intraepidermal blisters
5. Keratinocytes exhibit marked intracellular vacuolization and dense clumps of keratin intermediate filaments (KIFs)
6. A mild perivascular lymphohistiocytic infiltrate is usually present in the upper dermis

Collectively, these histopathologic changes are described as "epidermolytic hyperkeratosis"

Electron microscopy:

- fragmented, clumped KIFs in the lower epidermis
- perinuclear KIF shells in the upper epidermis.

Molecular diagnosis:

- Mutation screening and complete sequencing of KRT1 and KRT10
- Prenatal diagnosis can be performed when the underlying mutation has been identified in affected family

Differential Diagnosis

In the neonatal period (blisters and erosions)

1. the presence of blisters and erosions differentiates EI from non-bullous congenital ichthyoses
2. various forms of **epidermolysis bullosa**
3. **staphylococcal scalded skin syndrome**
4. other **vesiculobullous** and erosive disorders that can present in neonates
   - (skin biopsy specimens and cultures)

later during infancy and childhood, EI must be distinguished from other congenital ichthyoses
- history of blistering (at birth and focal recurrences) and cutaneous superinfections
- the distinctive histologic features
- Although it may also be seen in .. epidermolytic palmoplantar keratoderma

Epidermolytic hyperkeratosis:
1. Epidermolytic ichthyosis
2. Epidermolytic nevi
3. Epidermolytic palmoplantar keratoderma

Treatment

Treatment is **symptomatic** and should be adapted to the **age** of the patient and **clinical issues.**

In the **neonatal** period,
- management in an **intensive care** nursery to provide
- protective **isolation**
- prevent or treat **dehydration, electrolyte** imbalance and cutaneous **superinfection**
- **Sepsis** should be treated with broad-spectrum antibiotics
- the neonate should be **handled carefully** with use of protective **padding** and **lubricants** (⇨ erosions and denuded skin usually heal rapidly)

In **children and adults**, therapy is aimed at
- reducing hyperkeratosis
- removing scale
- softening the skin

Topical treatment:
1. **Keratolytic** creams and lotions containing urea, salicylic acid and α-hydroxy acids
   - Effective
   - not well tolerated, especially in children, because of burning and stinging
   - Widespread topical application of higher-concentration salicylic acid preparations should be avoided because of the risk of systemic salicylism

26/09

2. **Topical tretinoin and vitamin D preparations may be beneficial but often cause skin irritation.**

3. **Frequent use of emollients and humectants can be combined with hydration (e.g. soaking of the skin during bathing) and mechanical abrasion of keratotic skin (e.g. gentle scrubbing with a soft brush or sponges).**

Systemic treatment:

- **Oral retinoids** may dramatically reduce hyperkeratosis and the frequency of infections in patients with generalized EI, but they also increase epidermal fragility and blistering.
- Low initial doses with gradual increase and careful monitoring are advisable, with use of the lowest effective maintenance dose

General measures:

- Bacterial skin infections are common and often trigger blistering; they require topical or systemic antibiotic treatment.
- Use of antiseptics such as antibacterial soaps, chlorhexidine or dilute sodium hypochlorite baths may help to control bacterial colonization. Continuous preventive therapy (oral or topical antibiotics) should be avoided because of the risk of developing antibiotic resistance.
- Because of the increased skin fragility, it is also important to prevent mechanical trauma (e.g. by wearing comfortable clothing and shoes).

X Linked (R) → recessive = both 2 copies of gene must be affected to have the desease.

X Linked = gene on X chromosom

in ♂ XY → all diseased

لدنه هاخين نسخه تانيه من الجين علشان تعوض

in ♀ XX → carrier

لديظهر عليه المرض لدن في نسخه تانيه تشيلها

د كده كده بيظهر عليهم المرض
كان AD او XLR
دعن طريق البنات مش الولاد

♀ carrier XX

Normal ♂ XY

XX XY XX XY

½ الولاد مرضى	½ الولاد سليم
½ البنات تنقل المرض	½ البنات سا

تنقل المرض للولاد بنسبة ٥٠٪
والبنات حامله للمرض بنسبه ٥٠٪

diseased ♂ XY

XX XX XY XY

½ الولاد سليم	لاد مصاب
½ البنات حاملين للمرض	ن مصابه

تنقل المرض للولاد بنسبه ٥٠٪
" " البنات بنسبه ٥٠٪

ماتنسيش تكتبي عن آلامان المتن	Ichthyosis. Vulgaris.	Steroid sulfate deficiency
ode of inheritance.	AD.	XLR
)efect.	FLG	STS
ge of onset	short after birth	neonate
ex.	both.	♂only ♀ carrier
ic of scale	small, white, No fissure	larg brown.
s. feature	① Atopic D ② Keratosis pilaris ③ Liner palm	① cornial obacites ② Crypto chedism ③ ♂ testies
Pathology	hypogranulosa or absent	hypergranulosa.
Electron microscape.	* abnormal Kerato hyalin. * No dismosom	* Normal Kerato hyalin. * dismosome. presist.

(Exfoliative dermatitis)

Symptom & sign :) = (dx)

Erythroderma (redness) & scaling > 90%

Causes

Child → erythroderma Ichthyosis.

adult → Erythroderma AE

" Eczema.

" drug eruption

" psoriasis.

Treatment

* tt of the cause ? Fluid

* Hospitalization → ? protein intake, parenteral substitute

* tt of complication → high cardiac output.

~~Exfoliative dermatitis~~

II. Ichthyosiform syndromes

1. **Sjögren-Larssone syndrome** (AR): LI, Mental retardation, spastic paresis. The defect is an inborn error in lipid metabolism. There is a deficiency of the enzyme fatty alcohol: nicotinamide-adenine dinucleotide oxidoreductase enzyme. This leads to accumulation of fatty alcohol. A diet lacking natural fat and containing medium-chain triglycerides may be beneficial in some patients.
2. **Rud's syndrome**: Ichthyosis, hypogonadism, mental retardation and Acanthosis Nigricans.
3. **KID syndrome**: Keratitis, Ichthyosis, Deafness.
4. **Conradi's syndrome**: Ichthyosis (whorled pattern with underlying erythema followed by follicular atrophoderma), in association with cataracts, circatricial alopecia and contractures.
5. **Netherton's syndrome** (AR): Ichthyosis Linearis circumflexa, Trichorrhexis invaginata, Atopy.
6. **IBIDS syndrome (Tay's syndrome)**: Trichothiodystrophy (AR)
   NCIE, Brittle hair, Intellectual impairment, Decreased fertility, Short stature. These abnormalities appear to be due to a markedly deficient sulfur content of hair which reflects a marked decrease in the sulfur-rich hair matrix protein.
7. **Refsum's syndrome** (AR): Ichthyosis, cerebellar ataxia, peripheral neuropathy, retinitis pigmentosa. There is inability to degrade exogenous phytanic acid found in green vegetables → accumulation of phytanic acid .
   Histopathologically, neutral lipid containing droplets within basal keratinocytes. The epidermis is hyperproliferative.
   Treatment: Chlorophyl-free diet.
8. **CHILD syndrome** (XD): Congenital Hemidysplasia, Ichthyosiform erythroderma and Limb Defects.
9. **Dorfman-chanarin syndrome** (netural lipid storage disease) (AR): NCIE-like or collodion baby + Myopathy + cataracts + neurologic problems. Neutral lipid droplets may be found in epidermal cells and in leukocytes.

III. Related Disorders of Cornification

1. **Ichthyosis Linearis Circumflexa** (AR) present at birth or shortly after, showing extensive migratory polycyclic lesions of erythema and scaling (resembling psoriasis). Some areas show double-edged scale at the periphery. It persists through life. In 50% of the cases trichorrhexis invaginata is present "Netherton syndrome".
2. **Harlequin Ichthyosis** (AR): Rare, usually fatal. The child is born encased in thick, horny cuirass with deep fissures. Marked ectropion and eclabion are present.
3. **Erythrokeratodermia Variabilis** (AD), rare, starts in infancy. It has 2 types:
   A. Patches of erythema assuming circinate or geographic patterns. These are variable i.e. the lesions fluctuate, sometimes rapidly, in their configuration and extent.
   B. Persistent hyperkeratotic plaques develop in areas of erythema and in normal skin.

IV. Acquired Ichthyosis

1. **Malignancy** "paraneoplastic": Lymphomas mainly Hodgkin's dis., but may be with other lymphomas, multiple myeloma, carcinoma and Kaposi's sarcoma.
2. **Nutritional deficiencies**
   - Malnutrition
   - Vit. A

Defect: (more than one defect)

① **Transglutaminase-1** deficiency (because it is AR)

- due to deleterious mutations in both copies of the TGM1 gene

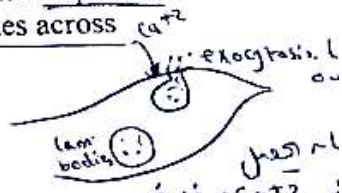
> **Transglutaminase-1 enzyme**
> - expressed in the upper differentiated layers of the epidermis
> - facilitates the formation of the cornified cell envelope by cross-linking numerous structural proteins (e.g. involucrin, small proline-rich proteins, loricrin, keratins and desmosomal proteins) to one another as well as to the lipid envelope

TGM1 mutations seriously disturb the complex process of cornification and desquamation.

② ~~Biallelic missense~~ mutations in the **ATP-binding cassette subfamily A member 12 gene (ABCA12)**

- this ABC transporter is found in **lamellar bodies** and responsible for the energy-dependent transport of lipid substrates across membranes

③ OTHER mutations.....



Clinical Features

Age of presentation: apparent **at birth**

Symptoms: severe disorder (bruising, disfigu)

Skin manifestations:

- Most affected neonates are encased in a **collodion membrane**
- Over the first weeks of life, the collodion membrane is gradually replaced by generalized **scales**
  - ⇨ large, brown, plate-like scales
  - ⇨ the scales are centrally attached and have raised borders, often leading to superficial fissures
- minimal to **no** associated **erythroderma** مهم جداً
- site: limbs, neck, face.

Other associated features:

- **Tautness of facial skin** commonly results in **ectropion, eclabium,** and significant **hypoplasia of nasal and auricular cartilage**
  - Severe ectropion may lead to **madarosis, conjunctivitis** and **incomplete lid closure** with ensuing **keratitis.**
- Traction and compression exerted by the taut skin can cause **scarring alopecia**, especially at the periphery of the scalp